

Pain Management for the Non-Pain Specialist

*Richard W. Rosenquist, M.D.
Associate Professor of Anesthesiology
Director, Pain Medicine Division
The University of Iowa Hospitals*

ABSTRACT:

The practice of pain medicine has seen a dramatic growth in the past 10 years. This is in part due to a societal recognition that the treatment of pain has value. It is also due to the progress made in numerous areas of research into pain mechanisms, pain treatments and the impact of good pain control. Anesthesiologists have played and continue to play a significant role in the treatment of pain of all varieties. The training may range from board certified specialists with fellowship training to individuals whose experience may consist of their pain rotation to those who are self-taught. Even in the setting where a fellowship trained pain specialist is unavailable, anesthesiologists are frequently asked to evaluate and treat patients with chronic pain from a variety of causes. Good fundamental treatment for a number of common pain conditions may be provided locally as long as good judgment is applied and referrals are made as necessary.

The traditional forms of pain treatment performed by anesthesiologist have included a variety of injections at various sites and for various purposes. Before performing any type of treatment, the anesthesiologist as physician is obligated to obtain a complete medical history, perform a physical examination and review any pertinent imaging studies to determine the etiology of the patient's pain. This is crucial in order to avoid complications due to a lack of sufficient information. This is also vital so that the anesthesiologists practicing pain medicine does not perform a block at the request of another physician without first deciding whether or not the procedure is appropriate for that particular patient. Finally, the anesthesiologist should be familiar with the alternative treatments for a given painful condition so that informed consent can be obtained prior to performing a procedure.

The discussion below will outline some of the major issues concerning the treatment of some common pain syndromes that an anesthesiologist is frequently asked to treat.

Neuropathic Pain

Neuropathic pain may result from a wide spectrum of insults to the peripheral or central nervous system. This may include nutritional deficiencies, systemic diseases, chemotherapy, cerebrovascular accident, surgery or trauma (see Table 1). The hallmark of neuropathic pain is abnormal neural activity in peripheral nerve(s) or the central nervous system. This is often accompanied by disordered sensory processing both in the peripheral or central nervous system. Even in injuries which are primarily peripheral in their location, the central nervous system often becomes involved. This group of painful disorders is one of the most challenging and difficult to treat. In a small number of cases, the patients may achieve complete relief of pain or actual recovery from the initial insult. However, in many more cases, pharmacologic management merely serves to help to control the symptoms or to minimize their day-to-day impact. In many other cases, despite therapeutic levels of pharmacologic agents, there is no relief of pain. The difficulty in treating these syndromes reflects both our poor understanding of the pathophysiologic

processes which lead to neuropathic pain as well as the limited usefulness of many of our pharmacologic agents. An improved understanding of the pathophysiology of neuropathic pain as a result of laboratory research as well as novel means of delivering currently available drugs have provided us with an improved ability to treat certain types of neuropathic pain. Despite these advances, neuropathic pain remains extremely challenging to treat in the best of hands.

Definitions

There are numerous words, which are used to describe the unusual sensations experienced by patients who have neuropathic pain. In order to clarify these terms and to be certain that we are discussing the same type of pain, the following definitions are offered.

Allodynia – Pain due to a stimulus that does not normally provoke pain.

Dysesthesia – An unpleasant abnormal sensation, whether spontaneous or evoked.

Hyperalgesia – An increased response to a stimulus that is normally painful. May also include decreased pain threshold.

Hyperesthesia – Increased sensitivity to stimulation excluding the special senses.

Hyperpathia – A painful syndrome, characterized by increased reaction to a stimulus, especially a repetitive stimulus, as well as an increased threshold.

Neuralgia – Pain in the distribution of a nerve or nerves.

Neuritis – Inflammation of a nerve or nerves.

Neuropathy – A disturbance of function or pathological change in a nerve, mononeuropathy; in several nerves, mononeuropathy multiplex; if diffuse and bilateral, polyneuropathy.

Nociceptor – A receptor preferentially sensitive to a noxious stimulus or to a stimulus that would become noxious if prolonged. Avoid pain receptor or pain pathway.

Pain – An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.

Paresthesia – An abnormal sensation, whether spontaneous or evoked.

Pathophysiology of Neuropathic Pain

Neuropathic lesions can begin in the periphery or in the central nervous system. In those patients in whom the syndrome begins in the periphery, it is believed that changes may occur in the spinal cord dorsal horn secondary to the constant barrage of neural traffic from the injured nerve. As the central nervous system processing is altered, larger myelinated fibers develop the ability to mediate abnormal nociceptive signals. This is thought to explain in part the development of light touch and thermal hyperalgesia as well as the allodynia that is seen in many patients with neuropathic pain syndromes.

Peripheral neuropathies may be the result of nerve compression. Nerve compression may lead to structural and functional changes in both the nerve and in the dorsal root ganglion in the spinal cord. Nerve section or significant lesion is followed by Wallerian degeneration. This period of Wallerian degeneration may be associated with a loss of sensation in the distribution of the nerve. As the nerve begins to regrow, it can do one of two things. If the nerve sheath is disrupted, the attempts of the nerve to reinnervate its normal pathway may result in the development of a neuroma. On the other hand, if the nerve sheath is intact, the growth cone may find its way to the original innervation pattern and the tissue trophic factors can support it. This recovery process may be associated with a traveling Tinel's sign as the tip proceeds toward the target. The regenerating tip of a nerve whether the nerve sheath is intact or disrupted develops many properties which are not seen in normal nerve. The growth tip or neuroma, depending on which situation is present, has exquisite mechanical sensitivity, which may be the result of a build up of mechanosensitive ion channels. It also becomes highly sensitive to catecholamines, which is very different from normal nerve. As a result, the growth tip or neuroma may be activated by increased sympathetic input.

The peripheral terminals of primary afferent nerves contain numerous peptides and fast transmitters in secretion granules. The presence of these compounds and secretion granules suggest that they may have an efferent function as well. There are some conditions, such as antidromic invasion of an action potential in which these secretion granules are released. The chemicals which are released include glutamate, CGRP, substance P, cytokines, arachidonic acid derivatives and nitric oxide. All of these agents are vasoactive to some degree and their release frequently results in redness and edema. These mediators may also sensitize adjacent nociceptive fibers resulting in spreading hyperalgesia. This symptom complex is often referred to as neurogenic inflammation. This is all accomplished in the absence of any sympathetic nervous system involvement. The resulting redness, swelling and pain, which are frequently seen with RSD or complex regional pain syndromes type I or II, may explain why this diagnosis is made so often.

In the face of peripheral nerve injury, changes may occur in the dorsal horn as well. Spontaneous activity within the peripheral nerve and the dorsal ganglion may lead to wind up mechanisms and sprouting of large A-beta fibers from deep lamina into more superficial layers. Sympathetic fibers sprout from within the dorsal root ganglion to form basket-like formations around the A-fiber cells. Degeneration of the GABA and glycine inhibitory cells within the dorsal horn occurs and results in unrestricted and undampened responses to A-beta fibers. In addition, the sprouting within the dorsal horn and spreading sensitization of dorsal horn neurons in the absence of any inhibition will lead to a widening of the receptor fields for dorsal horn neurons. This results in spread of pain away from the site of injury, a situation frequently encountered in neuropathic pain.

Some of the increase in spontaneous activity observed in the dorsal horn may be due to an increased release of glutamate or sensitization of the NMDA glutamate receptor or both. Anatomical, electrophysiological and behavioral studies suggest that glutamate is one of the most important transmitters of excitation between the primary afferent and spinal neurons involved in pain processing, and that antagonists of glutamate receptors therefore might be useful analgesics. The major drawback is the ubiquity of glutamate in central nervous system functions. NMDA receptor antagonist administration is frequently associated with adverse reactions. Recent studies have suggested a role for other classes of glutamate receptors such as AMPA/Kainate. AMPA/Kainate receptor blockade has been demonstrated to reduce spinal neuron sensitization that mediates capsaicin-evoked pain and allodynia with a low incidence of side effects. The new understanding of the AMPA/Kainate receptors have begun to modify the viewpoint of the role of the NMDA receptor. These areas remain promising with respect to the development of new treatments for neuropathic pain syndromes.

Many of the changes which occur in the spinal cord may be reversible in response to a loss of the afferent traffic which lead to their initial development. Many therapies for neuropathic pain are aimed at suppressing the signals of the nerve that is injured in the periphery. Suppression of these signals over an extended period of time may allow reversion to a more normal state of sensory processing within the spinal cord. Much more disturbing, however, is the fact that the longer the pain state persists without any type of treatment, the less likely significant improvement will occur in the patient.

Basic Principles of Treatment

Patients who have neuropathic pain may report a wide variety of unusual sensations or pain complaints. These may include burning pain, pain radiating into an area of anesthesia, or an absent limb, pulling, drawing or crawling sensations, lancinating explosive pains which may be spontaneous in their origin or induced by mechanical or thermal stimulation. Despite the bewildering array of symptoms, each patient warrants a complete diagnostic evaluation in order to look for a treatable cause for their neuropathic pain complaint. These patients will have frequently seen many different physicians before presenting to a pain medicine clinic. They may or may not have been worked up appropriately prior to their arrival to the pain clinic. The pain medicine practitioner is obligated to perform a complete history and physical examination. The potential for developing a specific diagnosis and treatment plan during this process should always be kept in mind. Unfortunately, many of the patients who present to pain clinics have neuropathic pain problems which are difficult to classify at best and have no specific diagnosis. As a result, we are limited to treating symptoms rather than specific disease processes. The severity of these pain complaints and their persistence frequently results in other problems which include physical dysfunction, psychosocial stressors, as well as other medical and psychological comorbidities. These areas should not be ignored when developing a treatment plan.

The history of a neuropathic pain problem is critically important and may give clues to the origin of the problem. If the patient presents with a history of abrupt focal onset of pain, this may be the result of a focal injury mechanism, such as ischemia, hematoma or mechanical compression resulting from a screw or suture. Neuropathic pain that has a slow onset of focal pain may be the result of fibrous compression due to healing surgical wound or trauma site. Patients may also have peripheral neuropathies due to ischemic compression that results from placement of a retractor against the nerve. In these settings, there may be a period of insensation preceding the onset of pain. Any period of lost sensation should be specifically investigated as part of the history. This is often a subtle change for the patient and may be obscured by the pain associated with a healing wound. Diffuse burning pain problems involving bilateral distal structures are consistent with a metabolic polyneuropathy, such as a diabetic neuropathy or neuropathy induced from chemotherapeutic agents or dietary insufficiencies.

Injuries to nerves which are more proximal or in the truncal regions of the body may often be described with descriptive terms which are in keeping with visceral pain. The patient may choose words such as muscle cramping or deep organ cramping. These symptoms should not be confused with true visceral pathology and patients should be carefully guarded against unnecessary surgical procedures.

Because of the challenges associated with treating many neuropathic pain problems, a careful discussion should be held with each patient at the initiation of the diagnostic and treatment process. Although patients will frequently present with expectations of a cure, this is frequently impossible to achieve. As a result, it is critically important that the patient have an understanding of the process of diagnosis and treatment, and a realistic set of expectations with regard to treatment outcomes. Patients should be advised in advance that they will frequently be required to trial many different medications in order to come up with an

appropriate combination of medications that will help to control or treat their symptoms. In addition, the medications which are used to treat neuropathic pain frequently have high side effect profiles. In some cases, a drug which is effective in controlling their neuropathic pain may be impossible to use secondary to the side effects of the medication.

Pharmacologic Therapy

The pharmacologic treatment of neuropathic pain incorporates many different classes of drugs. Each of the different classes has found some use in treating neuropathic pain. Frequently a process of trial and error is required in order to come up with the most effective single drug or combination of drugs in order to treat neuropathic pain with a minimum of side effects. These drug classes can include opiates, antidepressants, antispasmodics, antiseizure agents, benzodiazepines, topical agents, psychotropic agents and others.

Opiates

Although opiates are not ideal drugs for the treatment of neuropathic pain, they are frequently used either alone or in conjunction with other medications to help treat the pain of neuropathic injury. Some patients will receive no benefit whatsoever from the opiate medications and will rapidly discontinue their use. Issues related to the appropriate use of narcotics and the risk of addiction are always present. Patients frequently feel that if they are only given enough opiates, their pain will go away. There are numerous studies outlining the successful use of opiates in the treatment of certain neuropathic pain problems. The opiate pain medications have included fentanyl, morphine, vicodin, oxycodone, methadone and others. Although these medications should not be considered first line agents for neuropathic pain, they should not be ignored.

Tramadol

Tramadol is an atypical opioid that has the characteristics of a weak mu opiate receptor agonist combined with weak norepinephrine and serotonin reuptake inhibition to produce synergistic analgesic action. There are some studies to suggest this medication has a role in the treatment of neuropathic pain. This medication is associated with less constipation, respiratory depression and abuse as compared to traditional opiates. It also lacks the anticholinergic effects seen in tricyclic agents. The most common side effects include nausea, sedation, dizziness and occasional seizures. The starting dose is 50 mg po q 6 hours on a PRN basis and may be increased to a total dose of 100 mg q 6 hours. Because of its association with seizures, it should not be given in excess of its maximum recommended dose and should not be used in patients with a history of seizures. It should be used in caution in patients concomitantly receiving tricyclic or SSRI antidepressants.

Antidepressants

Antidepressants have been widely used in the treatment of neuropathic pain. Although numerous studies support their use in the treatment of neuropathic pain, the exact mechanism of their action is unclear. They are not given in doses sufficient to relieve depression. They are frequently used to produce improvement in sleep patterns. It is postulated that catecholamine uptake may account for some of the action, but it appears as if the effects of these compounds on norepinephrine is the most important. The serotonin agents have not demonstrated the same degree of efficacy for treating neuropathic pain as have the tricyclic antidepressants. The tricyclic agents include amitriptyline, imipramine, desipramine, nortriptyline and

doxepin. Amitriptyline represents the most widely study antidepressant for pain. It is useful in neuropathic, visceral and headache pain conditions. It has the highest side effect profile with significant anticholinergic, α -adrenergic blocking and antihistaminic effects. It inhibits both norepinephrine and serotonin reuptake in neurons. Amitriptyline has a significant sedative effect. Patients taking amitriptyline may experience a hung-over effect the day after taking the drug initially. This hang-over effect will frequently diminish over time. These medications may also be associated with an increase in appetite and/or weight. Nortriptyline is the active metabolite of amitriptyline and has less cardiovascular stimulation or sedation. It is a relatively pure norepinephrine blocker and may be associated with nightmares in some patients. The non-tricyclic agents include trazodone. This drug is primarily a serotonin uptake blocker and is very sedating. It does not have the anticholinergic or α -adrenergic blocking activities of the tricyclics. It is a useful drug for producing improvements in sleep patterns in patients who otherwise do not tolerate tricyclic agents. Trazodone is notable for an active metabolite that is a serotonin receptor agonist and has the side effect of priapism. There is little evidence for true effectiveness of Trazodone in the treatment of neuropathic pain. Venlafaxine is a new agent that has significant norepinephrine uptake activity, but has not been well defined in terms of its role in the treatment of neuropathic pain. Fluoxetine, paroxetine and sertraline are new antidepressant agents. They are markedly different from the older drugs and do not carry nearly their side effect profile. They have a potent effect on serotonin involvement. However, good studies regarding their results in the treatment of neuropathic pain are lacking.

Anticonvulsant Agents

The anticonvulsant agents are a structurally diverse group of compounds with no known common mechanism of action. This class of medications is used for a wide variety of neuropathic pain complaints. In general, the anticonvulsants are thought to decrease neural membrane excitability and to increase the threshold for activation.

Carbamazepine. Carbamazepine is structurally related to imipramine and may have some antidepressant properties. The most widely recognized mechanism of action is due a decrease in neuroma or ectopic neural activity due to an inhibition of sodium and potassium conductance. Although this medication is frequently effective, its use is limited by a wide range of side effects which include ataxia, sedation, nausea and diplopia. In addition, it has the potential for affecting bone marrow and liver. Associate a hepatic enzyme elevation is reversible and should be monitored on a routine basis. In addition, its results on bone marrow function should be monitored as well. These concerns are most effectively addressed by obtaining baseline and frequent hematologic and liver function studies at the initiation of therapy or when changing doses of carbamazepine. Dosing should be initiated at a dose of 100 mg po BID and gradually increased at 4-5 day intervals. Suggested serum levels of this medication range been 4-12 mcg/ml.

Clonazepam. Clonazepam is useful both as an antiseizure agent and as a treatment for neuropathic pain. It is thought to act by increasing the inhibitory effectiveness of GABA in the spinal cord dorsal horn to suppress incoming nociceptive activity. This compound has no active metabolites and has a long serum half-life, which allows it to be dosed once a day. Typical doses range from 0.5-3 mg per day. Because sedation is a side effect, it is most frequently initiated with a dose of 0.5 mg at bedtime. Side effects may include sedation, ataxia and personality changes. Because of its benzodiazepine character, any decision to discontinue therapy with this medication should be planned with a slow withdrawal.

Phenytoin. Phenytoin is capable of exerting analgesic effects through a local anesthetic mechanism of membrane stabilization in neuromas and damaged nerves. Support for the utilization of phenytoin for the

treatment of neuropathic pain is minimal and it is not frequently used as a first-line drug. In addition, its potential for significant drug interactions and distressing side effects have limited its use.

Gabapentin. Gabapentin is one of the most widely used anticonvulsants for the treatment of neuropathic pain at the present time. It is thought to work by binding to a subunit on the voltage dependent calcium channel, which is distinct from standard calcium channel blockers. By inhibiting calcium influx into the nerve terminal, less neurotransmitters are released. Gabapentin may also inhibit glutamate synthesis and inhibit GABA breakdown. Both of these effects would inhibit primary afferent transmission of nociceptive information. Gabapentin has some significant advantages over other anticonvulsants. It is not metabolized in the liver and is excreted unchanged in the kidney. It is not associated with changes in the bone marrow and liver, and as a result, blood monitoring is not necessary with this medication. Dosing is typically started at 100 mg po TID and gradually increased to a maximum level of 900-1200 mg TID. If higher doses are needed, then an additional dosing period will need to be initiated as this drug suffers from dose-dependent bioavailability. This is due to its ability to saturate intestinal uptake. If the patient has renal failure, the dose will need to be reduced. This drug is often associated with side effects, including sedation, blurry vision or dizziness, which may limit its use. In addition, some patients report significant swelling with the use of gabapentin.

Lamotrigine. Lamotrigine exerts anticonvulsive effects similar to carbamazepine due to its ability to inhibit both independent sodium channels. It is typically dosed once per day and is associated with minimal hepatic effects and no known adverse effect on bone marrow. The most common adverse effect is an erythematous macular rash, which is more common in younger patients and with more rapid dose escalations. The drug may also be associated with GI disturbance, sedation and ataxia.

Antispasmodics

Baclofen. Baclofen is a GABA-b receptor agonist and is mostly used to suppress spinally mediated motor spasticity seen in patients with spinal cord injuries. Baclofen is most effective in incidental lacerating pain states or episodic pain. In episodic pain, the GABA receptors are relatively unoccupied and the addition of baclofen can affect the suppression of primary afferent activity and dampen an excitable focus. Baclofen can be very sedating and can alter cognition. In addition, abrupt withdrawal has been associated with seizures.

Topical Agents

Capsaicin. Capsaicin is an extract of hot peppers. When injected or applied topically, it may cause direct stimulation and eventual degeneration of small unmyelinated sensory fibers. Capsaicin acts through a vanilloid receptor which regulates nonspecific ion channels. The mechanism of capsaicin action is excitotoxicity, specifically on unmyelinated fibers. Because excitation of the fibroids intrinsic to capsaicin's action, the use of local anesthetic by injection or topically will prevent the therapeutic effect of capsaicin. The toxic stimulation is accompanied by the release of primary afferent neurotransmitters including substance P, CGRP and others. Initial application of capsaicin cream may cause significant burning pain and flare, which decreases with repeated use.

Aspirin. Topical aspirin mixed with either ether or alcohol has been utilized in some patients with neuropathic pain. These include patients with post-herpetic neuralgia and other peripheral neuropathic pain syndromes.

Local Anesthetics

Local anesthetics may suppress the spontaneous activity of injured nerve via a topical administration, intravenous administration or, in some cases, an oral administration.

Lidocaine. Intravenous lidocaine infusions have been reported to relieve neuropathic pain and outlast the period of infusion. The reports of effectiveness have included low back pain, atypical facial pain, headache, diabetic or ischemic neuropathies and some complex regional pain syndromes. There is sufficient evidence to suggest that the response to this medication is not only dose related, but rate dependent. Those patients who receive the medication over a prolonged period of time will have no benefit whatsoever. There always remains the risk of significant local anesthetic toxicity, including tinnitus, perioral numbness, confusion, light headedness, tachycardia, convulsions, hypotension and occasionally bradycardia.

EMLA. Eutectic mixture of local anesthetics. This combination of local anesthetic crystals lowers the melting point of the other and allow the eutectic mixture to be developed. The eutectic mixture can be placed topically with result in local anesthetic effect developed underneath it. This has been effective in some peripheral neuropathic situations and in some patients with post-herpetic neuralgia. There is the potential for toxicity if too large an area is covered.

Mexiletine. Mexiletine is an orally active analog of lidocaine which has demonstrated effectiveness in some neuropathic pain states, such as diabetic or AIDS related neuropathies. The toxicity is similar to intravenous lidocaine. In addition, this medication has significant GI distress associated with it. Studies have demonstrated the GI distress in nearly 50% of patients who take this medication. It is frequently the adverse CNS effects and GI effects which limit the use of this medication.

Psychotropic Drugs

The psychotropic drugs may be utilized in some peripheral and central neuropathic pain states. These include drugs such as the phenothiazines and neuroleptics. They are frequently used in combination with opioid and non-opioid analgesics. The mechanism of action is thought to be dopamine receptor blockade. The side effect profile includes extrapyramidal symptoms, α_1 adrenergic blockade, antihistamine and anticholinergic activity.

Novel Delivery Systems

There are numerous drugs which have markedly different potencies or enhanced therapeutic ratios when administered epidurally or intrathecally. These include compounds such as opiates, baclofen or clonidine that may be administered either epidurally or intrathecally. These novel delivery sites are frequently capable of producing desirable results while minimizing the systemic side effects which are frequently noted with the larger doses required for systemic administration.

Conclusions

The neuropathic pain syndromes remain a very challenging part of pain medicine practice. The varied and unusual clinical presentation in combination with the numerous diagnostic possibilities make these syndromes difficult to diagnose and treat. There are patients in whom pharmacologic management can produce successful results when combined with appropriate diagnostic testing, psychological and

rehabilitative support, and appropriate goals of the initiation of therapy. The latest research efforts into these difficult pain problems hold great promise for better diagnoses and treatment in the future.

Table 1.
Classification of Neuropathies
Usually Associated with Pain

Mononeuropathies

Trauma

Entrapment syndromes

Brachial plexitis/lumbar plexitis

Connective tissue disease

Postherpetic neuralgia

Carcinomatous neuropathy

Diabetic neuropathy

Diabetic amyotrophy

Polyneuropathies

Isoniazid neuropathy

Pellagra neuropathy

Fabry's disease

Dominantly inherited sensory neuropathy

Diabetic polyneuropathy

Amyloid neuropathy

Alcoholic neuropathy

Gullian-Barré neuropathy

Beriberi neuropathy

Strachan syndrome

Burning feet syndrome

Decompression sickness

Toxic neuropathies

Arsenic

Chloramphenicol

Metronidazole

Organophosphorus

Thallium

Misonidazole

Vincristine

Cis-platinum

Stroke

Spinal cord injury

Complex Regional Pain Syndromes

The Complex Regional Pain Syndromes Type I (formerly RSD) and Type II (formerly causalgia) are a complicated group of pain syndromes whose etiology is poorly understood. Patients will typically present with burning pain in a non-dermatomal pattern, allodynia, edema, temperature changes and autonomic changes following an injury. Other symptoms including decreased range of motion, sensory changes, weakness, muscle wasting, increased hair or nail growth and skin changes may be present. There are no perfect diagnostic tools for this disease process although response to sympathetic blockade, IV phentolamine infusion or the results of a triple phase bone scans have been used with some success. The use of sympathetic blockade to provide pain relief to facilitate pain relief and physical therapy has been a well-established part of conventional treatment. This may take the form of stellate ganglion blocks (using the C6 tubercle as a landmark), lumbar sympathetic blocks or anesthetics such as epidural or brachial plexus blockade. Other forms of treatment including IV regional blockade with local anesthetics and bretylium, IV phentolamine, epidural or intrathecal clonidine, topical capsaicin, TENS, IV calcitonin, spinal cord stimulation, and a wide variety of oral medications including vasoactive compounds, anti-depressants, anti-convulsants and analgesics. All of these treatments are ineffective if they are not combined with active physical therapy to maintain range of motion and strength of the affected limb. In addition, psychologic support is needed for many of these patients.

Herpes Zoster

The treatment of the pain associated with acute herpes zoster or post-herpetic neuralgia is very different. In the acute phase, treatment may frequently consist of oral steroids, anti-viral agents, opioid analgesics and tri-cyclic anti-depressants. There is research to suggest that early initiation of treatment with the tricyclic antidepressant amitriptyline may reduce the incidence of post-herpetic neuralgia. In addition, the performance of sympathetic blocks within one week after the eruption of the vesicles may be useful in preventing an irreversible ischemic insult to the affected nerve.

Pain occurring beyond the acute phase is extremely difficult to treat. It is associated with burning pain, hyperesthesia and allodynia. The mainstay of treatment is medical management. This may include tricyclic antidepressants, anticonvulsants, and oral anti-arrhythmics. TENS, topical capsaicin, and topical aspirin ether or chloroform have been used successfully in some patients. Occasionally, sympathetic blockade may provide relief. In the case of post-herpetic neuralgia involving the thorax or abdomen, epidural local anesthetic and steroid may provide some benefit in conjunction with medical therapy, although injection techniques are less useful in this phase.

Low Back and Neck Pain

Low back pain and neck pain are very common in the adult population. The natural history of these disorders is that this majority (>85%) will get better within six weeks. The percentage increases (>90%) within six months and the remainder may either require interventional treatment or progress to long term back problems.

A variety of injection therapies have been used in conjunction with other forms of treatment for low back and neck pain. These treatments include trigger point injections, epidural steroid injections, selective nerve root injections and facet injections.

Trigger point injections are useful in the treatment of myofascial pain syndromes. These patients have point tenderness, which consistently reproduces their pain. The pain is not always dermatomal and may also be associated with non-dermatomal complaints of numbness. These areas are localized and then injected with a local anesthetic. The local anesthetic is frequently combined with other compounds including steroids and NSAID's. The beneficial effects may in part be related to the pain relief of the local anesthetic, but may also be related to the myotoxic effects of the local anesthetic and any other additives.

Epidural steroid injections are useful in treating patients with pain due to nerve root irritation. These patients usually present with pain in a radicular distribution to an arm or a leg. It has been used effectively to treat pain due to intervertebral disc herniation or spinal stenosis. It is most effective in patients with symptoms for six months or less, no prior history of spine surgery and clear clinical signs of nerve root inflammation. An MRI imaging study is quite useful to determine if the history and physical exam correlate with demonstrable anatomic findings and to avoid needle placement into or an area in the patient with spinal stenosis where there is little or no epidural space. The absence of MRI findings, which correlate with the history and physical examination, does not always rule out a role for epidural steroids. A leak of phospholipase A-2 and other enzymes from the nucleus pulposus may produce a chemical root irritation with signs of mechanical compression. Ideally, the injection should be performed at the level of the root irritation to maximize the concentration of the steroid in the affected area. Eighty milligrams of methylprednisolone or triamcinolone is usually injected in a total volume of 10 cc of saline. The addition of a local anesthetic may be useful in the patient with severe pain in muscle spasm. Good clinical outcome data on the use of epidural steroids is lacking, although larger multicenter trials are underway which may provide valuable evidence for the technique.

PHYSICAL SIGNS OF NERVE ROOT IRRITATION

ROOT	INTERSPACE	MOTOR	REFLEX	SENSATION
C5	C4 - 5	Biceps Abduct Arm	Biceps	Deltoid
C6	C5 - 6	Finger Flexion		Volar surface of hand
C7	C6 - 7	Triceps muscle	Triceps	Dorsum of the hand
C8	C7 - T1	Interosseus muscles of the hand		Half of the fourth and all of the fifth digit
L3	L3 - 4	Knee extension	Knee jerk	Anterior thigh
L4	L4 - 5	Inversion	Knee jerk	Medial foot
L5	L5 - 5	Dorsiflexion		Dorsum/lateral foot
S1	L5 - 5	Eversion	Ankle jerk	2nd, 3rd, 4th toes

In the lumbar region, the practitioner should be aware that the location of the disc will determine which nerve most is symptomatic at any given level e.g. L3-4 lateral disc = L3 nerve root, L3-4 central disc, L4 = nerve root.

Selective nerve root block has been advocated in place of epidural steroid injections for the treatment of radiculitis. A paravertebral approach to the nerve root using fluoroscopic guidance allows direct access to the nerve root. This alternative approach to the nerve root not only allows direct delivery of the steroid medication, but also may provide additional diagnostic information confessing the source of pain if the pain is relieved after local anesthetic injection.

Facet syndrome occurs when degenerative disk disease or excessive stress produces subluxation of the posterior elements resulting in arthritis of the facet joints. Injection of local anesthetic and corticosteroid into the facet joints under fluoroscopic guidance can provide diagnostic information and therapeutic benefit. Frequently a series of these injections is performed every few weeks for a maximum of three in six months.

Patients who respond well to these interventions have specific tenderness over the facet joints, radiographic evidence of facet disease, lack neurologic findings in extremities, and have pain with hyperextension maneuvers. If long term benefits are not obtained with local anesthetics/steroid injections, radiofrequency ablation or cryoablation techniques of the medial branch supplying the facet joints may be performed although the results of these techniques are mixed.

Cancer Pain

The vast majority of cancer patients experience pain as the disease becomes more advanced. Direct tumor invasion produces the majority of this pain. However, many patients have pain as a result of cancer therapies such as surgery, radiation therapy and chemotherapy. Some treatments for pain are directed at control of the tumor or debulking. Aside from those treatments aimed directly at the tumor, there are a number of other options available to treat the pain associated with cancer.

The majority of patients with cancer pain are able to obtain good pain relief with systemic analgesics alone. A sound guideline for the use of analgesics in cancer pain can be found in the AHCPR guidelines for cancer pain treatment. These are similar to the WHO guidelines as well.

If cancer related pain, initiate the analgesic ladder:

Non-opioid +/- adjuvant

Opioids for mild to moderate pain + non-opioid +/- adjuvant

Opioid for moderate to severe pain +/- non-opioid +/- adjuvant

Reassessment

If the patient has persistent pain

Consider other etiologies and treatments

Non-steroidal anti-inflammatory drugs may be useful in combination with opioids. This is especially true in patients with pain of bony or inflammatory origin. A variety of other adjuvant drugs including antidepressants, anticonvulsants, oral anti-arrhythmics and corticosteroids are useful for treating patients with nerve invasion, compression or other neuropathic pain syndromes.

When opioids are used for pain control, the side effects should be treated aggressively in order to maximize the benefit of the expense of the side effects. Nausea may be treated with the phenothiazines, butyrophenones or Ondansetron. Constipation may be treated with a variety of dietary agents as well as medications. Excessive sedation may be treated with an AM dose of an amphetamine. Some patients develop untreatable side effects at doses of opioids adequate to control their pain. These patients may be candidates for intraspinal opioids in order to minimize the dose required to treat pain and to limit the systemic side effects. If this technique appears to be indicated, a trial infusion may be performed using a conventional epidural catheter. If this catheter is placed epidurally, the dose via the catheter should be 5-10% of the daily systemic dose. If the catheter is intrathecal, the dose through the catheter should be .5 - 1.0% of the daily systemic dose. Patients suffering from intractable neuropathic pain may benefit from the addition of clonidine to epidural or intrathecal delivery systems.

There are a variety of systems available for the long-term infusion of intraspinal opioids. These range from implantable catheters with externalized ports to implanted subcutaneous infusion pumps. The cost varies widely depending on the complexity of the system. For this reason, permanently implanted pumps are seldom recommended for patients with a life expectancy of less than six months.

Neurolytic procedures involving the use of alcohol, phenol, cryoablation or radiofrequency ablation may be very useful in the treatment of cancer related pain. Intrathecal or epidural neurolysis may be very useful for pain involving the trunk where the risk of motor weakness or bowel and bladder dysfunction is reduced. These techniques may also be quite useful when the tumor is invading a neuroforamina and it is the only way to block the nerve proximal to the insult. Perhaps the most useful technique is the celiac plexus block. This technique provides good to excellent pain relief of upper abdominal visceral pain, especially in the center of pancreatic cancer. When performed early in the course of the disease, it may prolong survival as well. Peripheral neurolysis carries a significant risk of neuritis, but may be useful for localized peripheral pain.

This outline reviews some of the common injection therapies performed in the setting of cancer. In most cases, the injection treatments alone are not sufficient to treat the pain of cancer as there are many factors which contribute to the overall situation. Referral of patients to large, multidisciplinary pain centers for neuroablative procedures may minimize the risk to the patients. In addition, access to the psychological support and multidisciplinary input needed for patients with severe multifactorial chronic pain problems will potentially improve their outcome.

Acute Postoperative Pain

Management of acute pain is essential from both the humanitarian and the physiologic standpoint. Ethically, all patients deserve to have their pain managed physiologically. Adequate analgesia may blunt the surgical stress response that includes increased heart rate, increased ability, decrease immune function and decrease gastrointestinal motility. In patients who have thoracic or upper abdominal surgical procedures or trauma, pulmonary function can be compromised because of reflexes splinting.

A combination of low dose local anesthetic and opioid infused in the epidural space has a certain effect to produce profound analgesia. Epidural infusion following aortic aneurysm repair may decrease cardiac morbidity and mortality. Epidural anesthesia/analgesia for total hip replacement is associated with decreased deep vein thrombosis and pulmonary embolism postoperatively. Epidural infusions following thoracic or upper abdominal procedures are associated with decreased incidences of postoperative pneumonia, respiratory failure and atelectasis. In patients undergoing cholecystectomy, postoperative epidural infusion of local anesthetic and opioid is associated with an earlier return of bowel function and earlier discharge from the hospital. With regard to immune function, studies have shown that epidural analgesia was associated with a decreased incidence of pneumonia, sepsis, and wound infections. Side effects of epidural narcotics would include respiratory depression, nausea/vomiting, pruritis, and urinary retention. However, these side effects may not be significantly different from those seen with IV PCA opioids.

REFERENCES

Abram S: Risk versus benefit of epidural steroids. *APS J* 1994; 3(1): 28-30.

Abdi S, Lee DH, Chung JM. The anti-allodynic effects of amitriptyline, gabapentin, and lidocaine in a rat model of neuropathic pain. *Anesth Analg* 87:1360-1366, 1998.

American Pain Society. Principles of analgesic use in the treatment of acute pain and chronic cancer pain: a concise guide to medical practice. Skokie, IL: American Pain Society; 1992.

Attal N, Brasseur L, Parker F, Chauvin M, Bouhassira D. Effects of gabapentin on the different components of peripheral and central neuropathic pain syndromes: A pilot study. *Eur Neurol* 40:191-200, 1998.

Backonja MM, Galer BS. Pain assessment and evaluation of patients who have neuropathic pain. *Neurol Clin* 16:775-790, 1998.

Baldomero M, Olivera et al: Diversity of Conus neuropeptides. *Science* 1990; 249:257-63.

Bennett GJ. Neuropathic pain: New insights, new interventions. *Hosp Pract* 33:95-98, 101-104, 107-110, 1998.

Benolt PW: Reversible skeletal muscle damage after administration of local anesthetic with and without epinephrine. *J Oral Surg* 1978; 36:198-201.

Bowsher D. Neurogenic pain syndromes and their management. *Br Med Bull* 47:644-666, 1991.

Breitbart W. Psychotropic adjuvant analgesics for pain in cancer and AIDS. *Psycho-Oncology* 7:333-345, 1998.

Brose WG, Gutlove DP, Luther RR, Bowersox SS, McGuire D: Use of intrathecal SNX-111, a novel, N-type, voltage sensitive, calcium channel blocker, in the management of intractable brachial plexus avulsion pain. *Clin J Pain* 1997; 13:256-9.

Buchser E, Goddard M, Heyd B, Joseph JM, Favre J, de Tribolet N, Lysaught M, Aebischer P: Immunisolated xenogenic chromaffin cell therapy for chronic pain. Initial clinical experience. *Anesthesiology* 1996; 85:1005-12.

Byas-Smith MG, Max MB, Muir J, Kingman A. Transdermal clonidine compared to placebo in painful diabetic neuropathy using a two-stage 'enriched enrollment' design. *Pain* 60:267-274, 1995.

Calodney AK, Olsen ML, Novy D: Fibromyalgia and myofascial pain syndrome. *Pain Digest* 1992; 2:142-7.

Campbell JN, Meyer RA. In: Primary Afferents and Hyperalgesia, Spinal Afferent Processing. Yaksh TL (ed). New York, Plenum Press, 1986, pp. 59-81.

Campbell JN, Raja SN, Meyer RA. Painful sequelae of nerve injury. Proceedings of the Vth World Congress on Pain. Dubner R, Gebhart GF, Bond MR (eds). Amsterdam, Elsevier Science Publishers BV (Biomedical Division), 1988, pp. 135-143.

Carpenter RL. Does outcome changes with pain management? ASA Refresher Courses in Anesthesiology. Barash PG, Deutsch S, Tinker J (eds). Lippincott-Raven Publishers, Philadelphia, PA, 1995, 23(3), pp. 29-41.

Chabal C, Jacobson L, Mariano A, Chaney E, Britell CW. The use of oral mexiletine for the treatment of pain after peripheral nerve injury. *Anesthesiology* 76:513-517, 1992.

Chaplan SR, Malmerg AB, Yaksh TL. Efficacy of spinal NMDA receptor antagonism in formalin hyperalgesia and nerve injury evoked allodynia in the rat. *J Pharmacol Exp Ther* 280:829-838, 1997.

Chaplan SR, Pogrel JW, Yaksh TL: Role of voltage-dependent calcium channel subtypes in experimental tactile allodynia. *J Pharmacol Exp Ther* 1994; 269:1117-23.

Chapman V, Suzuki R, Chamarette HL, Rygh LJ, Dickenson AH. Effects of systemic carbamazepine and gabapentin on spinal neuronal responses in spinal nerve ligated rats. *Pain* 75:261-272, 1998.

Dahl JB, Rosenberg J, Hansen BL, Hjortsø, Kehlet H. Differential analgesic effects of low-dose epidural morphine and morphine-bupivacaine at rest and during mobilization after major abdominal surgery. *Anesth Analg* 74:362-5, 1995.

Dayer P, Collart L, Desmeules J. The pharmacology of tramadol. *Drugs* 47(supple 1):3-7, 1994.

Dellemijn PL, van Duijn H, Vanneste JA. Prolonged treatment with transdermal fentanyl in neuropathic pain. *J Pain Symptom Manage* 16:220-229, 1998.

Dickenson AH, Sullivan AF. Differential effects of excitatory amino acid antagonists on dorsal horn nociceptive neurons in the rat. *Brain Res* 506:31-39, 1990.

Di Vadi PP, Hamann W. the use of lamotrigine in neuropathic pain. *Anaesthesia* 53:808-809, 1998.

Dougherty PM, Willis WD. Modification of the responses of primate spinothalamic neurons to mechanical stimulation by excitatory amino acids and an N-methyl-D-aspartate antagonist. *Brain Res* 542:15-22, 1991.

Eide PK, Jorum E, Stubhaug A, Bremnes J, Breivik H. Relief of post-herpetic neuralgia and the N-methyl-D-aspartic acid receptor antagonist ketamine: A double-blind, cross-over comparison with morphine and placebo. *Pain* 58:347-354, 1994.

Eisenach JC, Du Pen S, Dubois M, et al: Epidural clonidine analgesia for intractable cancer pain. The Epidural Clonidine Study Group. *Pain* 1995; 61:391-399.

Elliott KJ. Taxonomy and mechanisms of neuropathic pain. *Semin Neurol* 14:195-205, 1994.

Ertas M, Sagduyu A, Arac N, Uludag B, Ertekin C. Use of levodopa to relieve pain from painful symmetrical diabetic polyneuropathy. *Pain* 75:257-259, 1998.

Foster AH, Carlson BM: Myotoxicity of local anesthetics and regeneration of the damaged muscle fibers. *Anesth Analg* 1980; 59:727-36.

Fromm GH. Baclofen as an adjuvant analgesic. *J Pain Symptom Manage* 9:500-509, 1994.

Galer BS. Neuropathic pain of peripheral origin: Advances in pharmacologic treatment. *Neurology* 45:S17-25, 1995.

Galer BS, Harle J, Rowbotham MC. Response to intravenous lidocaine infusion predicts subsequent response to oral mexiletine: A prospective study. *J Pain Symptom Manage* 12:161-167, 1996.

Gostine M, Treatment of cancer patients with epidural butamben. Presented at the Tenth World Congress of Anaesthesiologists; 1992; The Hague.

Grond S, Radbruch L, Meuser T, Sabatowski R, Loick G, Lehmann KA. Assessment and treatment of neuropathic cancer pain following WHO guidelines. *Pain* 79:15-20, 1999.

Hassenbusch SJ, Stanton-Hicks M, Covington EC, Walsh JG, Guthrey DS. Long-term intraspinal infusions of opioids in the treatment of neuropathic pain. *J Pain Symptom Manage* 10:527-543, 1995.

Hegarty A, Portenoy RK. Pharmacotherapy of neuropathic pain. *Semin Neurol* 14:213-224, 1994.

Hwang JH, Hwang KS, Leem JK, Park PH, Han SM, Lee DM. The antiallodynic effects of intrathecal cholinesterase inhibitors in a rat model of neuropathic pain. *Anesthesiology* 90:492-499, 1999.

Idanpaan-Heikkila JJ, Guilbaud G. Pharmacological studies on a rat model of trigeminal neuropathic pain: Baclofen, but not carbamazepine, morphine or tricyclic antidepressants, attenuates the allodynia-like behaviour. *Pain* 79:281-290, 1999.

Inturrisi CE, Colburn WA, Verebey K, Kayton HE, Woody GE, O'Brien CP. Propoxyphene and norpropoxyphene kinetics after single and repeated doses of propoxyphene. *Clin Pharmacol Ther* 31:157-167, 1982.

Jacox A, Carr DB, Payne R, et al: Clinical Practice Guideline: Management of Cancer Pain. Agency for Health Care Policy and Research. Publication No. 94-0592.

Janig W: Is the reflex sympathetic dystrophy a neurological disease? In: Janig W and Schmidt RF (eds) *Reflex Sympathetic Dystrophy: Pathophysiological Mechanisms and the Clinical Implications*. CH Weinheim; 1992.

Jarvis B, Coukell AJ. Mexiletine. A review of its therapeutic use in painful diabetic neuropathy. *Drugs* 56:691-707, 1998.

Kaiko RF, Foley KM, Grabinski PY, Heidrich G, Rogers AG, Inturrisi CE, Reidenberg MM. Central nervous system excitatory effects of meperidine in cancer patients. *Ann Neurol* 13:180-185, 1983.

Kehlet H. Postoperative pain relief -- what is the issue? *British Journal of Anaesthesia* 72(4):375-378, 1994.

Kingery WS. A critical review of controlled clinical trials for peripheral neuropathic pain and complex regional pain syndromes. *Pain* 73:123-139, 1997.

Kishore-Kumar R, Max MB, Schafer SC, Gaughan AM, Smoller B, Gracely RH, Dubner R. Desipramine relieves postherpetic neuralgia. *Clin Pharmacol Ther* 47:305-312, 1990.

Klepstad P, borchgrevink PC. Four years' treatment with ketamine and a trial of dextromethorphan in a patient with severe post-herpetic neuralgia. *Acta Anaesthesiol Scand* 41:422-426, 1997.

Levy MH: Pharmacologic Treatment of Cancer Pain. *NEJM* 1996; 15:1124-32.

Lipman AG. Analgesic drugs for neuropathic and sympathetically maintained pain. *Clin Geriatr Med* 12:501-515, 1996.

Lodge D, Headley PM, Curtis DR. Selective antagonism by D-alpha-amino adipate of amino acid and synaptic excitation of cat spinal neurons. *Brain Res* 152:603-608, 1978.

Lynn B. Review article: Capsaicin: Actions on nociceptive C-fibres and therapeutic potential. *Pain* 41:61-69, 1990.

MacFarlane BV, Wright A, O'Callaghan J, Benson HA. Chronic neuropathic pain and its control by drugs. *Pharmacol Ther* 75:1-19, 1997.

Makin MK, Ellershaw JE. Substitution of another opioid for morphine. Methadone can be used to manage neuropathic pain related to cancer. *BMJ* 317:81, 1998.

Mao J, Price DD, Caruso FS, Mayer DJ: Oral administration of dextromethorphan prevents the development of morphine tolerance and dependence in rats. *Pain* 1996; 67:361-8.

Miljanich GP, Ramachandran J: Antagonists of neuronal calcium channels: Structure, function and therapeutic implications. *Ann Rev Pharmacological Toxicol* 1995; 35:707-34.

Martin LA, Hagen NA. Neuropathic pain in cancer patients: Mechanisms, syndromes, and clinical controversies. *J Pain Symptom Manage* 14:99-117, 1997.

Max MB, Culnane M, Schafer SC, et al. Amitriptyline relieves diabetic neuropathy pain in patients with normal or depressed moods. *Neurology* 37:589-596, 1987.

Max MB, Kishore-Kumar R, Schafer SC, Meister B, Gracely RH, Smoller B, Dubner R. Clinical section: Efficacy of desipramine in painful diabetic neuropathy: A placebo-controlled trial. *Pain* 45:3-9, 1991.

Max MB. Towards physiologically based treatment of patients with neuropathic pain. *Pain* 42:131-133, 1990.

McGraw T, Stacey BR. Gabapentin for treatment of neuropathic pain in a 12-year-old girl. *Clin J Pain* 14:354-356, 1998.

McQuay HJ, Tramer M, Nye BA, Carroll D, Wiffen PJ, Moore RA. A systemic review of antidepressants in neuropathic pain. *Pain* 68:217-227, 1996.

Mercadante S, Lodi F, Sapio M, Calligara M, Serretta R. Long-term ketamine subcutaneous continuous infusion in neuropathic cancer pain. *J Pain Symptom Manage* 10:564-568, 1995.

Myers RR. 1994 ASRA Lecture. The pathogenesis of neuropathic pain. *Reg Anesth* 20:173-184, 1995.

Nelson KA, Park KM, Robinovitz E, Tsigos C, Max MB. High-dose oral dextromethorphan versus placebo in painful diabetic neuropathy and postherpetic neuralgia. *Neurology* 48:1212-1218, 1997.

Pan HL, Chen SR, Eisenach JC. Intrathecal clonidine alleviates allodynia in neuropathic rats: Interaction with spinal muscarinic and nicotinic receptors. *Anesthesiology* 90:509-514, 1999.

Pan HL, Eisenach JC, Chen SR. Gabapentin suppresses ectopic nerve discharges and reverses allodynia in neuropathic rats. *J Pharmacol Exp Ther* 288:1026-1030, 1999.

Pappas GD, Lazorthes Y, Bes JC, Tafani M, Winnie AP: Relief of intractable cancer pain by human chromaffin cell transplants: Experience at two medical centers. *Neurol Res* 1997; 19:71-7.

Park KM, Max MB, Robinovitz E, Gracely RH, Bennett GJ. Effects of intravenous ketamine, alfentanil or placebo on pain, pinprick hyperalgesia and allodynia produced by intradermal capsaicin in human subjects. *Pain* 63:163-172, 1995.

Payne R, Patt RB, Hill CS, eds: *Assessment and Treatment of Cancer Pain. Progress in Pain Research and Management. Volume 12; 1998. IASP Press.*

Richeimer SH, Bajwa ZH, Kahraman SS, Ransil BJ, Warfield CA. Utilization patterns of tricyclic antidepressants in a multidisciplinary pain clinic: A survey. *Clin J Pain* 13:324-329, 1997.

Robbins WR, Staats PS, Levine J, Fields HL, Allen RW, Campbell JN, Pappagallo M. Treatment of intractable pain with topical large-dose capsaicin: Preliminary report. *Anesth Analg* 86:579-583, 1998.

Rosen NB: The myofascial pain syndromes. *Phys Med Rehabil Clin North Am* 1993; 4:41-62.

Rosenberg JM, Harrell C, Ristic H, Werner RA, de Rosayro AM. The effect of gabapentin on neuropathic pain. *Clin J Pain* 13:251-255, 1997.

Rowlison J: Epidural steroids. *APS J* 1994; 3(1):20-7.

Rowbotham M, Harden N, Stacey B, Berstein P, Magnus-Miller L. Gabapentin for the treatment of postherpetic neuralgia: A randomized controlled trial. *JAMA* 280:1837-1842, 1998.

Sang CN, Hostetter MP, Gracely RH, Chappell AS, Schoepp DD, Lee G, Whitcup S, Caruso R, Max MB. AMPA/Kainate antagonist LY293558 reduces capsaicin-evoked hyperalgesia but not pain in normal skin in humans. *Anesthesiology* 89:1060-1067, 1998.

Shulman M, Lubenow TR, Rozanski-Dragasic LR, Ivankovich AD: Comparison of Coeliac plexus neurolytic block and epidural butamben injection for the control of pain from metastatic cancer of the pancreas. *Anesthesiol* 1995; 83(suppl 3A):A807.

Shulman M: Treatment of cancer pain with epidural butyl-amino-benzoate suspension. *Reg Anesth* 1987; 12:1-4.

Sindrup LH, Gram LF, Brosen K, Eshoj O, Morgensen EF. The selective serotonin reuptake inhibitor paroxetine is effective in the treatment of diabetic neuropathy symptoms. *Pain* 42:135-144, 1990.

Smith GD, Harrison SM, Birch PJ, Elliott PJ, Malcangio M, Bowery NG. Increased sensitivity to the antinociceptive activity of (+/-) baclofen in an animal model of chronic neuropathic, but not chronic inflammatory hyperalgesia. *Neuropharmacol* 33:1103-1108, 1994.

Snootsky SA, Jaeger B, Oye R: Prevalence of myofascial pain in general internal medicine practice. *West J Med* 1989; 151:157-60.

Steward JD. *Focal Peripheral Neuropathies*. New York, Raven Press, 1993.

Stubhaug A, Breivik H. Long-term treatment of chronic neuropathic pain with the NMDA (N-methyl-D-aspartate) receptor antagonist ketamine. *Acta Anaesthesiol Scand* 41:329-331, 1997.

Stubhaug A, Breivik H, Eide PK, Kreunen M, Foss A. Mapping of punctuate hyperalgesia around a surgical incision demonstrates that ketamine is a powerful suppressor of central sensitization to pain following surgery. *Acta Anaesthesiol Scand* 41:1124-1132, 1997.

Swerdlow M, Cundill JG. Anticonvulsant drugs used in the treatment of lancinating pain: A comparison. *Anaesthesia* 36:1129-1132, 1981.

Szallasi A, Blumberg PM. Vanilloid receptors: New insights enhance potential as a therapeutic target. *Pain* 68:195-208, 1996.

Tanelian DL, Brose WG. Neuropathic pain can be relieved by drugs that are use-dependent sodium channel blockers: Lidocaine, carbamazepine, and mexiletine. *Anesthesiology* 74:949-951, 1991.

Tolle TR, Berthele A, Schadrack J, Zieglgansberger W. Involvement of glutamatergic neurotransmission and protein kinase C in spinal plasticity and the development of chronic pain. *Prog Brain Res* 110:193-206, 1996.

Travell JG, Simons DG, eds: *Myofascial Pain and Dysfunction: The trigger Point Manual*. Baltimore: Williams and Wilkins; 1983, 3.

Watson CP, Babul N. Efficacy of oxycodone in neuropathic pain: A randomized trial in postherpetic neuralgia. *Neurology* 60:1837-1841, 1998.

Watson CP. The treatment of postherpetic neuralgia. *Neurology* 45:S58-60, 1995.

Westbrook GL. Glutamate receptor update. *Curr Opin Neurobiol* 4:337-346, 1994.

Woolf CJ, Thompson SW. The induction of maintenance of central sensitization is dependent on N-methyl-D-aspartic acid receptor activation: Implications for the treatment of post-injury pain hypersensitivity states. *Pain* 44:293-299, 1991.